

March 13, 2000

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fisher Lane, Room 1061
Rockville, MD 20852

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Re: Docket No. 99D-5199

Dear Sir or Madam:

The Adhesion Barrier Task Force, an *ad hoc* group consisting of manufacturers of adhesion barrier devices, is pleased to provide the following comments on the Food and Drug Administration's (FDA), "Draft Guidance for Resorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery" which was released for comment on December 16, 1999. The Adhesion Barrier Task Force is comprised of representatives from the following companies: Alliance Pharmaceutical Corp., Anika Therapeutics Inc., Biomatrix Inc., Confluent Surgical, Focal Inc., FzioMed, Genzyme Corporation, Gliatech, Lifecore, Life Medical Sciences, ML Laboratories, Cook, Synechion, and Target Health.

The Task Force is pleased that the FDA has taken the initiative to put forward a guidance document for adhesion barrier devices and thus acknowledges the agency's effort. We believe that this guidance document is an important step towards establishing consistent requirements for safe and effective adhesion barrier devices for both FDA and industry. Industry's interest and commitment towards this goal are reflected by the fact that this Task Force was formed within two weeks of FDA's notice in the Federal Register of the availability of the guidance document, and by the substantial amount of work involved in putting these comments together within a short period of time. It is the hope of the Task Force that this will result in a cooperative effort between industry and FDA towards the common goal of developing an adhesion barrier guidance document that provides both the least burdensome approach to device development, as well as sound medical and scientific rationales for the evaluation of the safety and effectiveness of such devices.

The Task Force welcomes the opportunity of furthering discussions with the FDA regarding this document. Our comments are intended to identify the key issues for further discussion and to provide suggestions to achieve a consensus. We look forward to collaborating with FDA in developing a comprehensive and consistent guidance document for adhesion barrier devices.

FDA Should Evaluate Adhesion Barrier Devices Only for the Proposed Label Claim:

One of the provisions of Section 205 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 (which adds to Section 515(d) of the Food, Drug and Cosmetic Act) limits FDA to review only the conditions of use in the proposed labeling of a premarket application (PMA) as the basis for determining whether a device is safe and effective. The reduction/prevention of adhesions is a legitimate label claim as it is possible to establish that a product can effectively reduce the development of adhesions. The Task Force is cognizant of the fact that a product label cannot make claims that are beyond what the product has been shown to do in the clinical trials. However, it is the position of the Task Force that it is appropriate for labels to state that the product has been shown clinically to reduce/prevent adhesions. Further, it is the position of the

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Task Force that clinical outcomes such as small bowel obstruction, pain, and infertility should not be required to be demonstrated in clinical trials as long as it is not claimed in the labeling. Therefore, FDA is limited by law to evaluate only the conditions of use submitted in the proposed labeling of the PMA, provided the proposed labeling is neither false nor misleading, and cannot require clinical outcomes that are not claimed by the sponsor in the labeling.

Adhesion Reduction as a Valid Clinical Endpoint:

The draft guidance document states that endpoints should optimally address clinical outcomes measures (e.g. decreased fertility, pelvic pain, or bowel obstruction). While the FDA accurately states that it is difficult to assess these types of clinical endpoints and that validated endpoints may sometimes be used, it is the opinion of the Task Force that the FDA is not addressing a very important point that was established in two separate General and Plastic Surgery Panel meetings. Specifically, panel members were asked whether adhesion prevention in and of itself is an important endpoint, and whether there was an implied claim of a clinical benefit beyond adhesion prevention when adhesion reduction/prevention was the sole endpoint (Seprafilm® and Sepracoat® panel meetings in 1996 and 1997, respectively). Both panels answered that adhesion prevention in and of itself is an important endpoint, that it was appropriate as an endpoint, that surgeons perform surgery to lyse adhesions, and therefore, that adhesion reduction/prevention is an appropriate and sufficient claim and endpoint.

Need for Least Burdensome Approach:

Another provision of Section 205 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 was intended to avoid over-regulation of devices and ensure that only the information necessary for a device's approval was required by FDA. Specifically, FDA was charged with determining the least burdensome means of product approval and market introduction. Currently, FDA and industry are working together to define "least burdensome" and to find ways to implement this FDAMA provision.

It is the opinion of this Task Force that the adhesion barrier guidance document, as it currently stands, does not represent the "least burdensome" means of evaluating adhesion barrier devices for their safety and effectiveness. The following are issues that have been identified by the Task Force as warranting further discussions with FDA and that, as currently stated, clearly demonstrate that FDA's understanding of "least burdensome" departs from Congressional intent.

Biocompatibility and Toxicity Testing:

The guidance document states that the amount of product used in biocompatibility and preclinical toxicity studies should reflect an appropriate safety margin compared to the doses proposed for use in humans, and that generally, doses at least 10 times the highest dose to be used in humans should be tested.

The Task Force acknowledges that preclinical toxicity studies should be conducted with product quantities that reflect an appropriate safety margin. However, the Sponsor should be allowed to justify the safety margin chosen in such tests. In addition, most biocompatibility tests defined in ISO 10993-1 already have pre-determined doses that are calculated by product surface area or weight. These test models do not generally allow for drastic increases in doses (for example cytotoxicity, muscle implantation, sensitization etc.). The following statement in the guidance

document should be removed: “Generally, doses at least ten times the highest dose to be used in humans should be tested.”

Pharmacokinetic Studies:

The FDA has suggested that absorption, distribution, metabolism, and excretion (ADME) studies should be conducted prior to initiation of clinical trials. This includes determining the fate of the metabolic components.

Traditionally, ADME studies have not been conducted for biodegradable polymeric devices such as sutures, hemostatic products, and adhesion barriers. As polymeric devices by nature, upon their degradation, form a number of potential breakdown products, it is extremely challenging to do drug ADME type studies on metabolic by-products. The Task Force supports what has been accepted in the past by the FDA for adhesion barrier devices, i.e. a description of the product’s primary route of distribution and clearance. Such studies should be complete at the time of PMA filing. All other references to ADME requirements should be omitted from the guidance document.

Performance Studies:

The guidance document recommends that performance studies be conducted in appropriate animal models to establish a reasonable premise that a product will be effective in humans. The implication is that, before performing clinical trials of a product to be used laparoscopically in humans, it should also prove effective in a laparoscopic animal model.

The Task Force agrees that it is important to evaluate a surgical product’s utility, ease of use and method of application in laparoscopy (if that is the intended means of use in a clinical trial). However, preclinical testing of effectiveness in both laparoscopic and open surgery animal models is unnecessary and would be overly burdensome. Animal models are intended to establish whether a product has feasibility of providing effectiveness by its intended mode of action. As laparotomy is considered to be more traumatic than laparoscopy, any adhesion barrier product shown to be effective in a laparotomy model should not be considered to be less effective in a laparoscopic model. Additionally, good laparoscopic animal models that would be predictive of human surgical outcomes are unknown, and the development of deployment tools solely for laparoscopic use in the animal model is unwarranted. Therefore, it is overly burdensome and unrealistic to require this excessive level of preclinical testing, when the real test is in the performance of the clinical trial. The Task Force feels it is sufficient to establish that a product works in an animal model looking solely at the mechanism of action, and suggests amending the language in the last statement of the “Performance Studies” section as follows: “A brief description of the rationale for and the limitations of the animal model should be included to address differences in the animal model and clinical use.”

Manufacturing:

In the sub-section for final product specifications, the guidance document suggests that levels of adhesion reduction in an animal model be included as a final product release specification.

The Task Force feels that including an animal performance assay is excessively burdensome to manufacturers and is unprecedented in the medical device industry. The Task Force knows of no other device that is required to pass an *in vivo* performance assay for lot release. The ability of

medical devices to perform their intended use is established in the design, manufacture, and preclinical and clinical testing of products, and data from such studies are included in the marketing application to the agency. It is the experience of the Task Force that a biological test is not quantitative, nor is it adequately reproducible to judge whether a product should be suitable for release. The specification of "level of adhesion reduction" should therefore be omitted.

Product Expiration/Testing:

The guidance document recommends that the incidence of *in vivo* adhesion reduction should be measured in product stability studies.

As with the final product specification requirement for *in vivo* product testing, The Task Force feels that this requirement is excessive and overly burdensome. The manufacturers support the use of animal testing for significant manufacturing changes and in the development of the product and product specifications. However, once a product has been established to be safe and effective in clinical trials and the manufacturing process has been established and shown to be reproducible by standard means, incorporation of an *in vivo* performance test and standard is redundant and an unnecessary use of experimental animals. The "incidence of *in vivo* adhesion reduction" should as a stability indicator should therefore be omitted.

Clinical Investigative Plan - Pivotal Studies - Hypothesis:

The guidance document suggests various examples for a study hypothesis.

The Task Force feels that reference to quantifying adhesion reduction (such as 75%) is arbitrary and should be removed from this section as it may prejudice future decisions on the level of adhesion reduction required for clinical trials. The study hypothesis may simply state that the level of adhesions in the treatment group will be statistically significantly lower than that in the control group. The percent reduction that is considered relevant should be mutually agreed upon by the Sponsor and FDA at the time of the study design.

Validated Endpoints:

The words "validated endpoints" and "clinically meaningful endpoints" are used throughout the clinical section of the guidance document, and the Task Force is concerned that they may cause confusion.

The Task Force believes that we understand what is meant by the FDA in using these terms, but would like to ensure clarity for future manufacturers and FDA reviewers of adhesion prevention devices. The Task Force understands that a "validated endpoint" means that the measure of adhesion reduction has been established and published in peer reviewed journals or has been determined during the conduct of the clinical trial. This would include establishing the accuracy, precision, robustness, and reproducibility of the primary outcome measure of adhesion prevention/reduction that was employed in the study. However, since there have been few, if any, reliable studies conducted establishing the quantitative connection between adhesion reduction and improvement in clinical outcomes, the Task Force feels that it is difficult to establish through a surrogate endpoint as to what is a "clinically meaningful endpoint." Because previous panels have established that adhesion prevention is an important outcome and the FDA has approved products based on adhesion reduction data, the Task Force feels that if the outcome of a trial

shows a significant reduction in adhesions, it should be sufficient for approval. The data for approval can be provided in the label so that physicians can determine the expected degree of effectiveness and the ability of the product to meet their acceptance criteria. The terms "validated endpoints" and "clinically meaningful endpoints" should be defined in the guidance document or omitted.

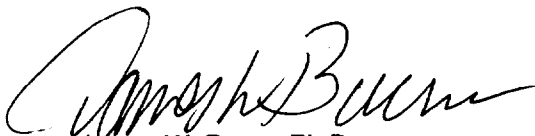
Clinical Outcomes:

The guidance document strongly suggests that, whenever possible, clinical outcomes be used as an indication of product effectiveness.

The Task Force agrees that specific outcomes measures, such as small bowel obstruction, pain, and infertility, are important to patients and clinicians for establishing the effectiveness of adhesion prevention barriers. However, the Task Force feels that it should be left to the Sponsor to electively select study endpoints and to pursue indications beyond the prevention of adhesions. Until there is more information and standards established for conducting these studies with highly specific clinical endpoints, it would be overly burdensome to suggest that measuring specific clinical outcomes might be the means of assessing product effectiveness as this has never been accomplished to date. Moreover, FDA's attempt to require additional claims is inconsistent with Section 205 of FDAMA that limits FDA to review only the conditions of use in the proposed labeling as the basis for determining whether a device is safe and effective. The reduction/prevention of adhesions is a legitimate claim, and attempts by FDA to go beyond this claim is contrary to what Congress intended in FDAMA. Currently, it is possible to measure adhesions in a reproducible way and to establish that a product can be effective in reducing adhesion development.

In conclusion, the Task Force would like to emphasize its wish to work closely with the FDA in revising the adhesion barrier devices guidance document and is willing to meet with representatives of the agency for further discussions and development of mutual understanding between the interested parties. We appreciate the opportunity to provide these comments and look forward to continuing this cooperative effort. Please feel free to call me or Naseem Kabir (617/374-7238) if you have any questions or require clarification.

Sincerely,



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For the Industry Adhesion Barrier Task Force

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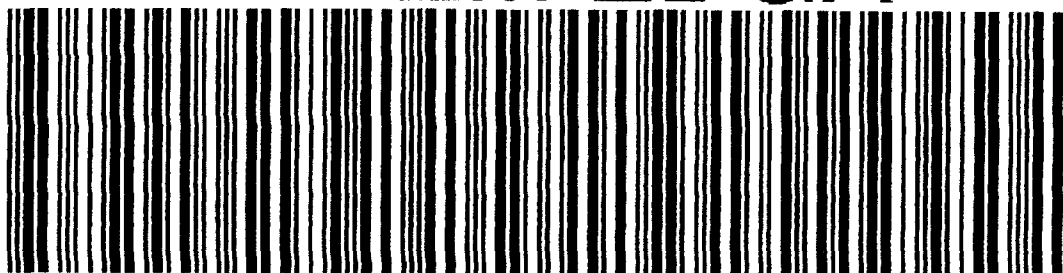
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